Data Analysis II: Quality of Life, Dementia, Memory and Global Index

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WHI Memory Study (WHIMS)

Shumaker, S.A., Reboussin, B.A.,Espeland, M.A., Rapp, S.R. (1998). The Women's Health Initiative Memory Study (WHIMS): A Trial of the Effect of Estrogen Therapy in Preventing and Slowing the Progression of Dementia. *Controlled Clinical Trials*, 19:604-621.

WHIMS Objectives

- To test the hypothesis that E+P will reduce incidence of:
  - Dementia (any cause)
  - Dementia caused by Alzheimer's Disease
  - Mild cognitive impairment
- To measure changes in cognitive functioning over time

Background

- Prevalence of all-cause dementia and Alzheimer's Disease increasing in general population; rates higher in women than men; no known therapies to effectively prevent or treat
- Cross-sectional, case-control and prospective studies support hypothesis that hormone therapy protects against development of dementia

HRT and Cognition
Systematic Review and Meta-Analysis

LeBlanc et al. JAMA 2001;285:1489-1499.

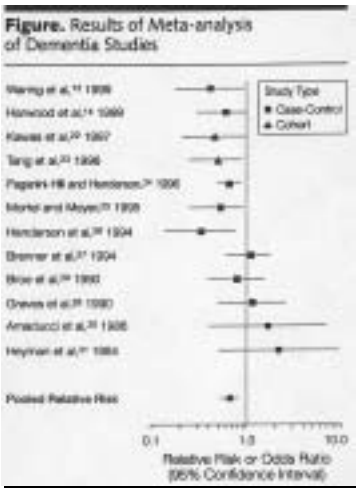
- 9 RCTs, 8 cohort studies of HRT and cognition
- No benefits in asymptomatic women
- Symptomatic women improved in some arenas:
  - verbal memory
  - vigilance
  - reasoning
  - motor speed
- Insufficient evidence on the effects of E+P

HRT and Alzheimer's Disease
Systematic Review and Meta-Analysis

LeBlanc et al. JAMA 2001;285:1489-1499.

- 2 cohort studies, 10 case-control studies
- RR from meta-analysis = 0.66 (CI 0.53-0.82)
- Studies may be influenced by poor proxy or subject recall or selection bias in HRT prescribing
- Results also subject to "healthy user" bias among women taking HRT
- No conclusions possible about progestins, estrogen doses or formulations

Results of Meta-analysis of Dementia Studies



Background

- RCTs in women with early dementia showed no benefit with respect to HT on symptom progression

Background

- Biological plausibility of estrogen's positive effect on cognition
  - Promotes cholinergic activity in the brain
  - Reduces accumulation of amyloid beta deposition
  - Reduces neuronal loss and stimulates axonal sprouting and dendritic spine formation
  - Reduces cerebral ischemia by improving blood flow
  - Modulates the expression of apoliproprotein E gene

WHIMS

- Approximately 7,500 non-demented women, 65-80 years old, with and without a uterus
- 39 clinical centers and WHI CCC
- 4,532 participants with a uterus in the WHIMS E+P trial

Baseline Characteristics and Adherence of WHIMS E+P Subtrial Participants

Variable	E+P N=2,229	Placebo N=2,303
Age, yr, N (%)		
65-69	1040 (46.7)	1081 (46.9)
70-74	779 (35.0)	829 (36.0)
75+	410 (18.4)	393 (17.1)
Education, N (%)		
< High school	150 (6.7)	148 (6.5)
High school/GED	446 (20.0)	498 (21.7)
> High school, < 4 yr college	894 (40.2)	870 (37.9)
> 4 yr college	734 (33.0)	779 (33.9)

Baseline Characteristics and Adherence of WHIMS E+P Subtrial Participants

History of stroke, N (%)	23 (1.0)	44 (1.9)
History of diabetes, N (%)	156 (7.0)	149 (6.5)
Prior hormone therapy, N (%)		
Any prior use	485 (21.8)	516 (22.4)
Prior use of estrogen only	305 (13.7)	323 (14.0)
Prior use of estrogen + progestin	222 (10.0)	236 (10.3)
Other prior medication use, N (%)	266 (12.0)	225 (9.8)
Statins (HMG-CoA reductase inhibitors)	627 (28.1)	682 (29.6)
Aspirin, regular use		

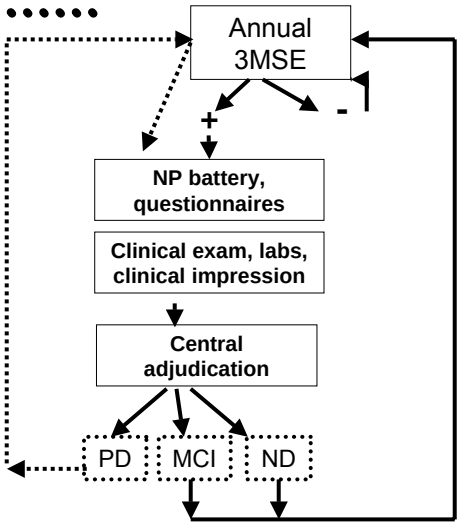
Baseline Characteristics and Adherence of WHIMS E+P Trial Participants

3MS total score at WHI enrollment		
Mean (SD)	95.45 (4.21)	95.62 (3.88)
Level, N (%)		
95 to 100	1535 (69.3)	1617 (70.9)
Above screening cutpoint1 to 94	534 (24.1)	544 (23.9)
At or below screening cutpoint	146 (6.6)	119 (5.2)
Adherence, N (%)		
Year 1	1496 (71.2)	1823 (83.3)
Year 2	1223 (60.5)	1534 (73.2)
Year 3	1087 (54.2)	1381 (66.3)
Year 4	899 (49.6)	1143 (61.0)
Year 5	364 (43.7)	507 (56.3)
Year 6	10 (32.3)	27 (61.4)

1Screening cutpoint was ≤ 80 for women with 0-8 years of formal education and ≤ 88 for women with 9 or more years of formal education.

WHIMS Methodology

- **Classification of PD returns annually for 3MSE, NP battery and questionnaires.**



WHIMS

- **Primary outcome: Dementia status**
  - No dementia
  - Mild cognitive impairment
  - Probable dementia

WHIMS

- **Secondary Outcome: Global Cognitive Functioning**

WHI Memory Study (WHIMS)

Global Cognition Results

Rapp, S.R., Espeland, M.A., Shumaker, S.A., et al. (2003). Effect of Estrogen Plus Progestin on Global Cognitive Function in Postmenopausal Women. The Women's Health Initiative Memory Study: A Randomized Controlled Trial. *JAMA*. Vol. 289, 20:2663-2672.

Definitions

- **Global Cognitive Function**

  Global cognitive function includes brain related abilities like attention, concentration, memory, language, abstract reasoning and calculation.

- **Normal Cognitive Aging**

  Age-related changes in cognitive processes, particularly verbal memory.

3MSE

- Domains
  - Orientation to time
  - Orientation to Place
  - Registration
  - Attention
  - Recall
  - Drawing
  - Naming
  - Repetition
  - Comprehension
  - Reading
  - Writing

3MSE Questions

1. “When were you born?”
   “Where were you born?”
2. “I am going to say three words for you to remember. Repeat them after I have said all three words: ‘shirt’, ‘brown’, ‘honesty.’”
3. “Now I would like you to count from 1 to 5.”
   “Now I would like you to count backwards from 5 to 1.”
4. “Spell world.”
   “Now, spell ‘world’ backwards.”

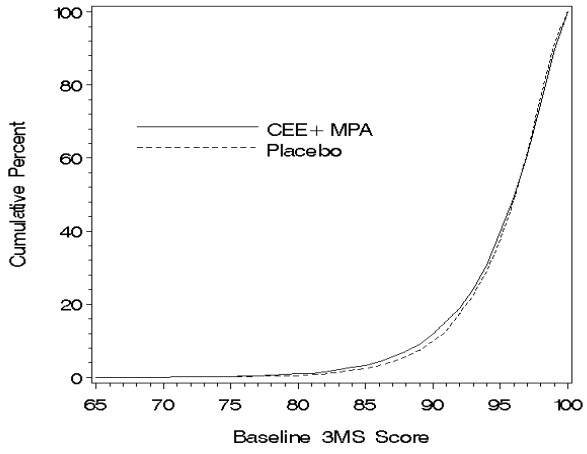
3MSE Questions

5. “What three words did I ask you to remember earlier?”
6. “What is today’s date?”
   “What day of the week is it?”
   “What season of the year is it?”
   “What state are we in?”
   “What country are we in?”
   “What city/town are we in?”
7. “Are we in a clinic, store, or home?”
8. “What is this [pencil]?”

3MSE Questions

9. “What animals have four legs?”
10. “In what way are an arm and a leg alike?”
    “In what way are laughing and crying alike?”
    “In what way are eating and sleeping alike?”
11. “Repeat what I say: I would like to go out.”
12. “Now repeat: No ifs, ands or buts.”
13. “Please do this.” [Close eyes]
14. “Please write the following sentence: I would like to go out.”

Baseline Distribution of 3MSE Scores

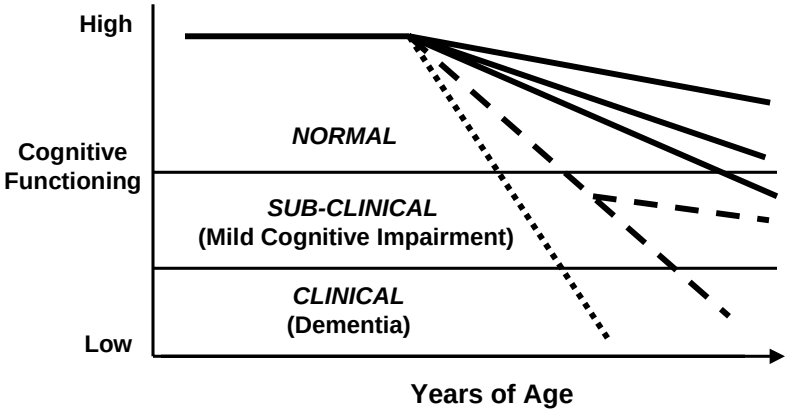


Baseline 3MSE Scores

	E+P	Placebo	P
Overall Score	95.50 ± 4.21	95.64 ± 3.87	0.26
Level			
95 to 100	1490 (69.9%)	1574 (71.1%)	
Cutpt[1] to 94	503 (23.6%)	525 (23.7%)	0.17
At/below cutpt	138 (6.5%)	114 (5.2%)	

[1]Cutpoint: ≤ 80 for 0-8 yrs education
≤ 88 for 9+ years education

Hypothetical Different Courses of Cognitive Functioning over Life Span



Longitudinal 3MSE

- Trajectories vary among participants
- Scores track within participants: Longitudinal r=0.82
- Analysis based on differences in annualized rates of change (Slopes)
- Women continue to contribute scores after diagnoses of probable dementia

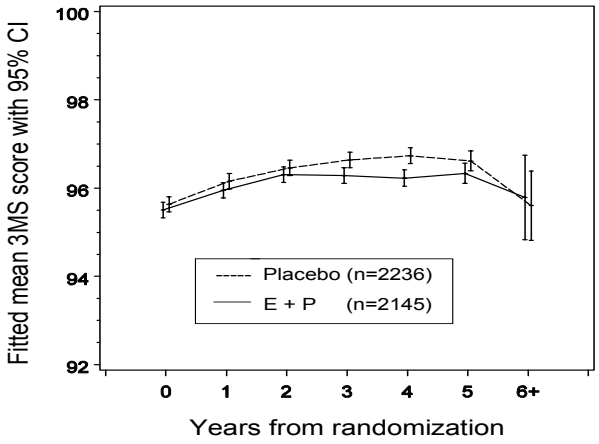
Statistical Methods

- Random coefficient (slope and intercept) mixed models
- Restricted maximum likelihood
- Intention to treat
- Nominal alpha=0.05 for primary comparison
- Bonferroni-adjusted subgroup analyses

Mean Rates of Change in 3MSE

E+P Mean (SE)	Placebo Mean (SE)	Difference Mean [95% CI] P-value
0.149 (0.021)	0.213 (0.020)	-0.063 [-0.120, -0.006] P=0.03

Mean 3MSE Scores Over Time

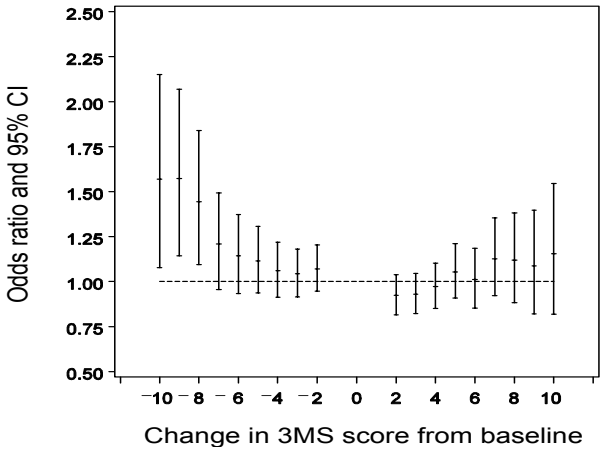


Consistency of Treatment Effects

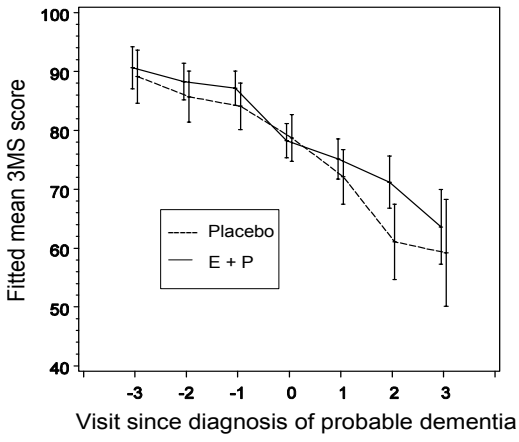
No marked differences in treatment effects were found across subgroups defined by

- SES (Age, education, ethnicity, income)
- Lifestyle (Smoking, alcohol, body mass)
- CVD risk (CVD history, hypertension, diabetes)
- Vasomotor symptoms, prior hormone use
- Therapy (aspirin, statins)
- Baseline 3MSE

Odds Ratio (95% CIs) By Magnitude of 3MSE Changes From Baseline



Mean 3MSE Scores (± Standard Error) Spanning Diagnoses of Probable Dementia



Primary Findings For Global Cognition

- E+P therapy was associated with a small adverse effect on global cognition over time
- Differences appeared to emerge after 2+ years
- Patterns of decline in 3MSE scores over time were similar between treatments among women classified with probable dementia

Conclusions From Global Cognition Analyses

- Results do not support use of E+P to protect cognition in older women
- Most women did not experience a negative effect from therapy, however a small increased risk of clinically meaningful cognitive decline occurred among women assigned to E+P

WHI Memory Study (WHIMS)

Dementia and Mild Cognitive Impairment Results

Shumaker, S.A., Legault C., Rapp S.R. et al. (2003). Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women. The Women's Health Initiative Memory Study: A Randomized Controlled Trial. *JAMA*, Vol. 289, 20:2651-2662.

What is Dementia?

- Age-associated memory inefficiency is not dementia
- Dementia: clinical syndrome characterized by a marked decline in memory and other thinking abilities that significantly interferes with daily functioning and that cannot be accounted for by medical or psychiatric causes.

What is Dementia?

- Most common cause, Alzheimer's disease, is gradual degeneration of brain cells (50% all dementias)
- Next most common cause, vascular disease, is damage resulting from blood blockages or bleeding in brain (30% all dementias)
- Dementia occurs in about 30%-50% of Americans over age 85

How is dementia diagnosed?

- Medical and neuropsychiatric evaluation
  - Rule out medical and psychiatric problems
  - Screen cognitive functions
  - Characterize signs and symptoms
  - Identify non-dementing illnesses, causes
- Detailed description of cognitive and behavioral changes by individual

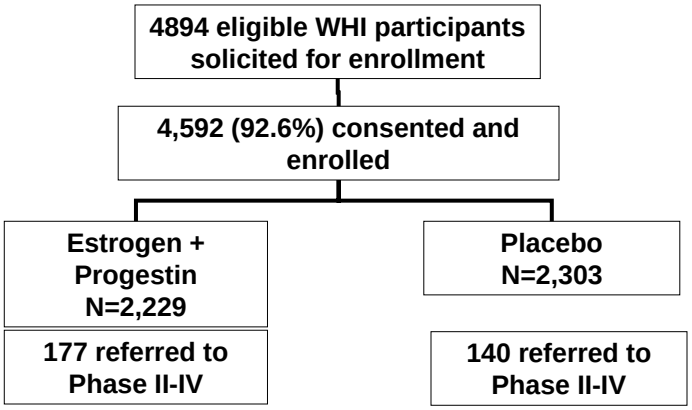
How is dementia diagnosed?

- Detailed description of cognitive and behavioral changes by reliable observer (family member)
- Comprehensive cognitive testing
- Laboratory exams (blood, brain scans)
- Monitoring of changes over time

What is Mild Cognitive Impairment?

- Perceived significant memory difficulty
- Below normal memory test performance
- Preserved overall cognitive functioning
- Preserved capability of carrying out basic activities of daily living
- Dementia syndrome ruled out
- ~15% of MCI cases develop dementia per year.

WHIMS Profile



WHIMS Participants

4,894 Age Eligible WHI Participants Solicited for Enrollment in WHIMS E+P trial

4,532 Provided Consent and Enrolled in WHIMS E+P trial
4,487 enrolled prior to WHI Randomization
8 enrolled 6 months after WHI Randomization
35 enrolled 6 to 18 Months after WHI Randomization
2 enrolled 18 to 24 Months after WHI Randomization

Estrogen+Progestin 2,229	Placebo 2,303
177 Participants Referred to Phases 2-4 (258 Referrals)[1]	**140 Participants Referred to Phases 2-4 (203 Referrals)[1]**
Status of Referrals as of July 8, 2002	**Status of Referrals as of July 8, 2002**
38 Participant refused further testing	**24 Participant refused further testing**
17 Incomplete data[2]	**17 Incomplete data[2]**
1 Participant deceased	**2 Participant deceased**
152 Adjudicated	**127 Adjudicated**
50 Not adjudicated[3]	**33 Not adjudicated[3]**

[1] A participant could be referred at any annual visit. [2] Data is incomplete because the participant did not return to the clinic for Phases 2-4 for reasons including lack of transportation, illness, family care giver responsibilities, scheduling conflict, etc. [3] 10% of all No Dementia and 50% of all MCI cases were adjudicated.

Assessment of Probable Dementia and Global Cognitive Function

- Phase I: Annual screener for mental status (3MS)
- Phase II: neuropsychological battery (CERAD)
  - verbal fluency (animal category)
  - naming
  - verbal learning and memory
  - constructional praxis
  - executive function

Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer disease. ***Neurology.*** **1989;39: 1159-1165.**

Assessment of Probable Dementia and Global Cognitive Function

- Phase III: physical and a neuropsychiatric exam by WHIMS certified geriatrician, neurologist, or geriatric psychiatrist

⇒Local adjudication based on Phase I-III

- ❑No dementia
- ❑Mild cognitive impairment
- ☑Probable dementia based on DSM-IV criteria

Assessment of Probable Dementia and Global Cognitive Function

- Phase IV: Rule out possible reversible causes of dementia
  - brain computerized tomography scan (without contrast)
  - laboratory blood tests

⇒final local determination based on Phase I-IV

⇒central adjudication based on Phase I-IV

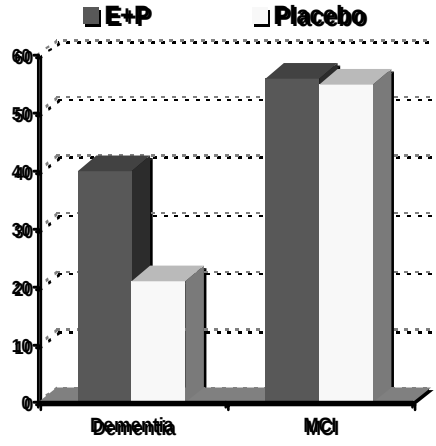
Statistical Methods

- Survival analyses: number of days from randomization into the WHI E+P trial to the date of the 3MSE that initiated the referral for additional cognitive testing resulting in the first post-randomization diagnosis
- Significance level of .05

WHIMS—Primary Results

	Estrogen+ Progestin	Placebo	Hazard Ratio	Nominal 95% CI
Probable Dementia	40 (0.45%)	21(0.22%)	2.05	(1.21,3.48)
Mild Cognitive Impairment	56 (0.63%)	55(0.59%)	1.07	(0.74,1.55)
PD or MCI	85 (0.95%)	66(0.71%)	1.37	(0.99,1.89)

Frequencies of Probable Dementia and Mild Cognitive Impairment Diagnosis



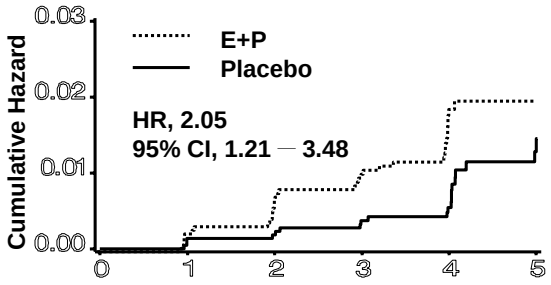
Dementia

- E+P group twice as likely to develop
- 23 excess cases per 10,000 person-years

MCI

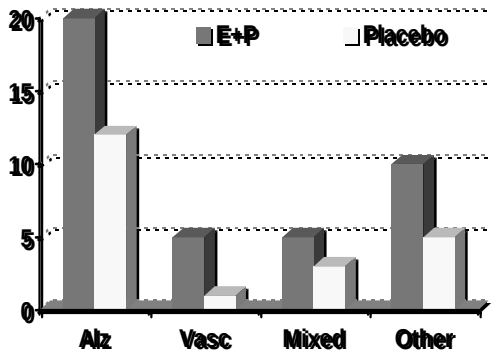
- No difference between groups

Probable Dementia Hazard Ratio



No. at Risk						
E + P	2229	2112	2026	1915	1325	401
Placebo	2303	2200	2125	1984	1392	477

Types (causes) of Dementia



- Alzheimer's dementia most common type
- E+P group higher number of cases for each type of dementia

Classification of Probable Dementia Cases

Dementia Type	E+P N=40 N (%)	Placebo N=21 N (%)
Vascular	5 (12.5)	1 (4.8)
Alzheimer	20 (50.0)	12 (57.1)
Other		
Mixed Type	5 (12.5)	3 (14.3)
Normal pressure hydrocephalus	2 (5.0)	0
Parkinson	0	1 (4.8)
Frontal lobe type	2 (5.0)	0
Alcohol related	1 (2.5)	0
Other dementia	3 (7.5)	2 (9.5)
Etiology unknown	2 (5.0)	2 (9.5)

Secondary Analyses for Probable Dementia

- When excluding 265 participants at higher risk for developing dementia at baseline (i.e. 3MSE score ≤ screening cutpoint), the hazard ration (HR) for probable dementia is 2.64 (95% CI, 1.26 – 5.53)
- When 2,534 non-adherent participants censored, HR for dementia is 3.22 (95% CI, 1.25 – 8.29)
- When censoring participants who starting using statins during the trial, HR for dementia is 1.93 (95% CI, 1.09 – 3/43)

Secondary Analyses for Probable Dementia

- In separate models, the interaction between treatment assignment and the following factors was not significant:
  - Age
  - Education
  - Smoking status
  - History of strokes
  - History of Diabetes
  - Prior hormone therapy use: any, E-alone, E+P
  - 3MSE total score at WHI enrollment
  - Adherence

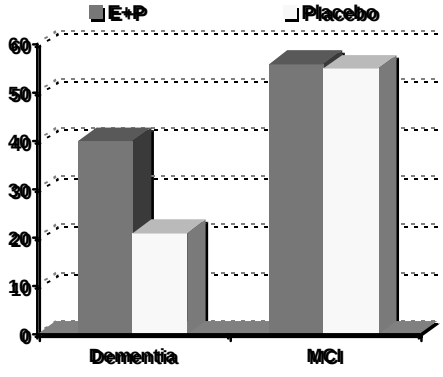
Secondary Analyses for Probable Dementia

- Main effects for age and 3MSE baseline scores were statistically significant, with higher risk of probable dementia in older women and in women with lower 3MSE baseline scores.

Diagnoses of Mild Cognitive Impairment: Frequencies and Rates for 10,000 Person-years

Outcome	E+P N = 2,229	Placebo N = 2,303	Hazard Ratio (95% CI)
Mild cognitive impairment	56	55	1.07 (0.74-1.55)
Mean (SD) follow-up (yrs)	3.99 (1.23)	4.04 (1.20)	
Rate per 10,000 person-years	63	59	

Frequencies of Probable Dementia and Mild Cognitive Impairment Diagnosis



Dementia

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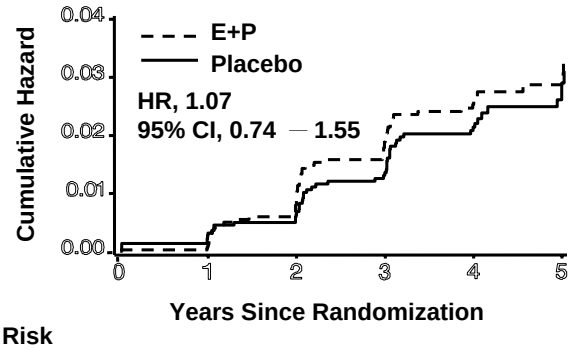
- 23 excess cases per 10,000 person-years

MCI

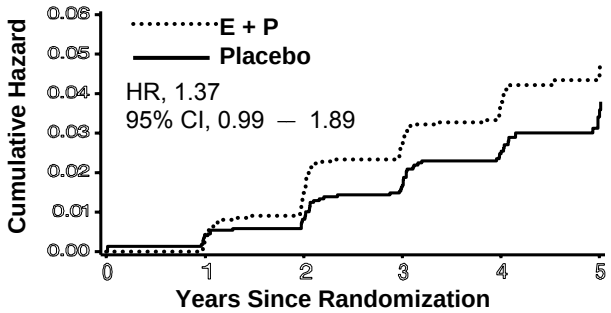
- No difference between groups

Mild Cognitive Impairment



No. at Risk						
E + P	2229	2112	2026	1915	1325	401
Placebo	2303	2200	2125	1984	1392	477

Probable Dementia or Mild Cognitive Impairment



No. at Risk						
E + P	2229	2112	2026	1915	1325	401
Placebo	2303	2200	2125	1984	1392	477

Primary Findings for Dementia and Mild Cognitive Impairment

- Risk of being diagnosed with probable dementia in the E+P group was twice that of women in the placebo group
- Groups began to diverge 1 year after randomization and differences continued through 5 years of follow-up
- Risk of being diagnosed with MCI was not statistically different between the two groups

Conclusions from Dementia and MCI Analyses

- Risk of probable dementia is 2.05 times higher with E+P therapy than with placebo
- E+P therapy did not prevent mild cognitive impairment
- These findings, coupled with previously reported WHI data, support the conclusion that the risks of E+P outweigh the benefits

Mechanism Issues

- Progestin role
- Timing, duration of use, mode and formulation
- E+P may accelerate underlying dementia
- E+P may initiate underlying mechanisms

Potential Limitations of WHIMS

- Cohort may not reflect general population
- Menopause occurred some years before enrollment
- Differential adherence: lower for E+P than placebo
- Sensitivity of 3MS to changes in cognition

What Does This Mean?

- Postmenopausal women around 65 and older:
  - Risks associated with combination hormone therapy clearly outweigh benefits
  - As women age, they are at higher risk for the diseases in the absence of combination hormone therapy – so should be particularly cautious
  - There is no reason for an older women to initiate or continue combination hormone therapy

What Does This Mean?, cont. .

- Postmenopausal women younger than 65:
  - Cannot generalize the dementia and cognitive functioning information to younger women – therefore, we cannot say whether there is increased risk, no effect, or a benefit
  - We can generalize the findings from last summer to younger women – that is, their risk for heart disease, stroke, breast cancer and blood clots is increased with combination hormone therapy

What Does This Mean?, cont. .

- Postmenopausal women younger than 65:
  - Until we more fully understand the full risks associated with combination hormone therapy, we recommend that when younger women consider using HT they do so only when they are suffering from severe menopausal symptoms and, in these cases, use HT for the shortest period of time at the lowest possible dosage.

Future Directions

- WHI E-Alone trial continues
- Follow-up of all E+P participants continues
- Mechanisms for risks & benefits
- Identification of women most at risk & most benefited

Quality of Life Outcomes in the Women's Health Initiative

Results of the randomized clinical trial of estrogen plus progestin

Health Risks and Benefits of E+P

- WHI Global Index was disease-based:
  - CHD, stroke, pulmonary embolism, breast cancer, hip fracture, colorectal cancer, endometrial cancer, death due to other causes
- Global risk index did not include health-related quality of life (HQOL)

WHI Quality of Life Study Primary Objective

- Test the effects of E+P on the following components of HQOL:
  - Perceived health and physical functioning, including pain
  - Mental health and depression
  - Energy and fatigue
  - Social functioning and limitations on role activities
  - Cognitive functioning
  - Sleep
  - Sexual satisfaction

Second Objective

- Assess whether E+P effects on HQOL differ in subgroups of women defined by:
  - Age
  - BMI
  - Vasomotor symptoms (hot flashes, night sweats)
  - Menopausal symptoms (vasomotor plus mood and cognition)
  - Prior use of hormones
  - CVD history
  - Sleep

Measures

- RAND-36 (0 to 100 range)
  - General Health
  - Physical Functioning
  - Role Limitation: Physical
  - Role Limitation: Emotional
  - Energy or fatigue
  - Bodily Pain
  - Social Functioning
  - Mental Health
  - Health Transition (1 item)
- Depression Score (-8.2 to 4 range)
- WHI Insomnia Rating Scale (0-20 range)
- Sexual Satisfaction (1-4 range)
- Modified Mini-Mental State Examination (3MS) (0-100 range)

HQOL Primary Results

- Three of 13 measures statistically significant
  - Physical functioning (0.8 difference/100 point scale)
  - Bodily pain (1.9 difference/100 point scale)
  - Sleep (.4 difference/20 point scale)
- Effect sizes below “small” (0.20-0.49)
  - Physical functioning = 0.06
  - Bodily pain = 0.09
  - Sleep disturbance = 0.11
- No differences after 3 years (n=1,511 women)

Statistical Challenges in HQOL Analyses

- Trial was overpowered to detect differences in HQOL continuous measures.
- Important to distinguish statistically significant but not clinically meaningful differences.
  - Effect sizes calculated and gauged against clinical norms.
- 13 treatment effects examined, 7 subgroups of interest
  - Bonferroni-corrected alpha levels used, nominal p-values reported

Calculation of Effects Sizes

$$d = \frac{M_{\text{estrogen+progestin}} - M_{\text{placebo}}}{S_{\text{placebo}}}$$

where M is the average difference in a HQOL measure and S is the standard deviation of the difference.

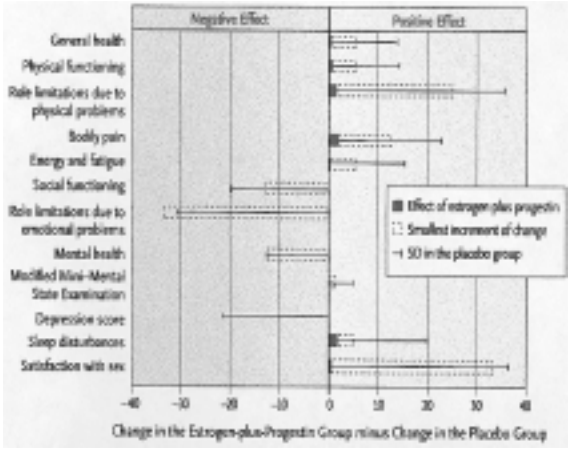
0.20-0.49 = small

0.50-0.79 = medium

>0.80 = large

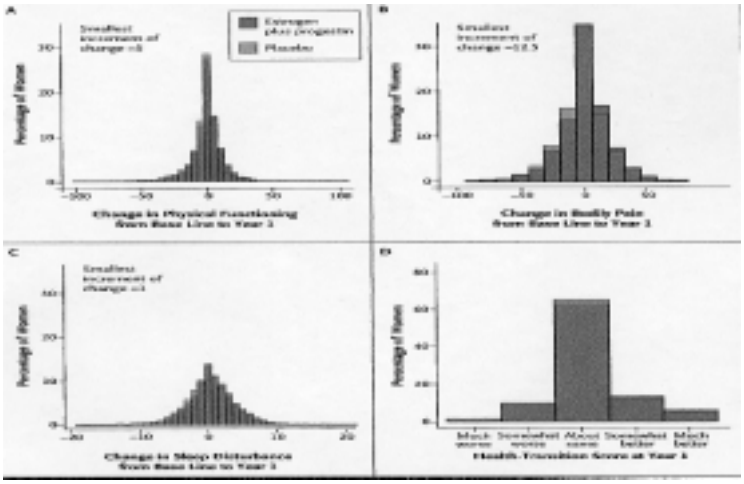
Source: Cohen J. Statistical power analysis for the behavioral sciences. 2nd Ed. Hillsdale, N.J.: L Erlbaum, 1988.

Differences in Quality of life change scores (Baseline to Year 1)



Hays J, Ockene J, Brunner R, et al. NEJM (2003)

Difference in Four Quality of Life Change Scores (Baseline - Yr 1)



Subgroup Differences Not Significant

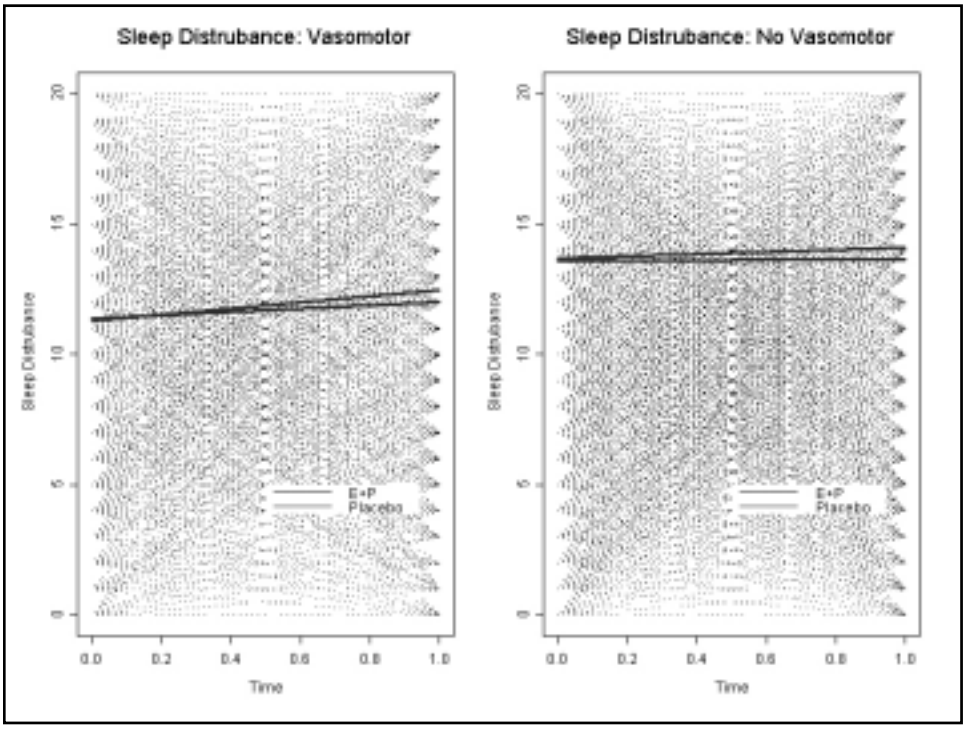
- No significant interactions with any baseline variable:
  - age
  - BMI
  - menopausal symptoms
  - sleep disturbances
  - prior HT use
  - CVD history
  - race/ethnicity

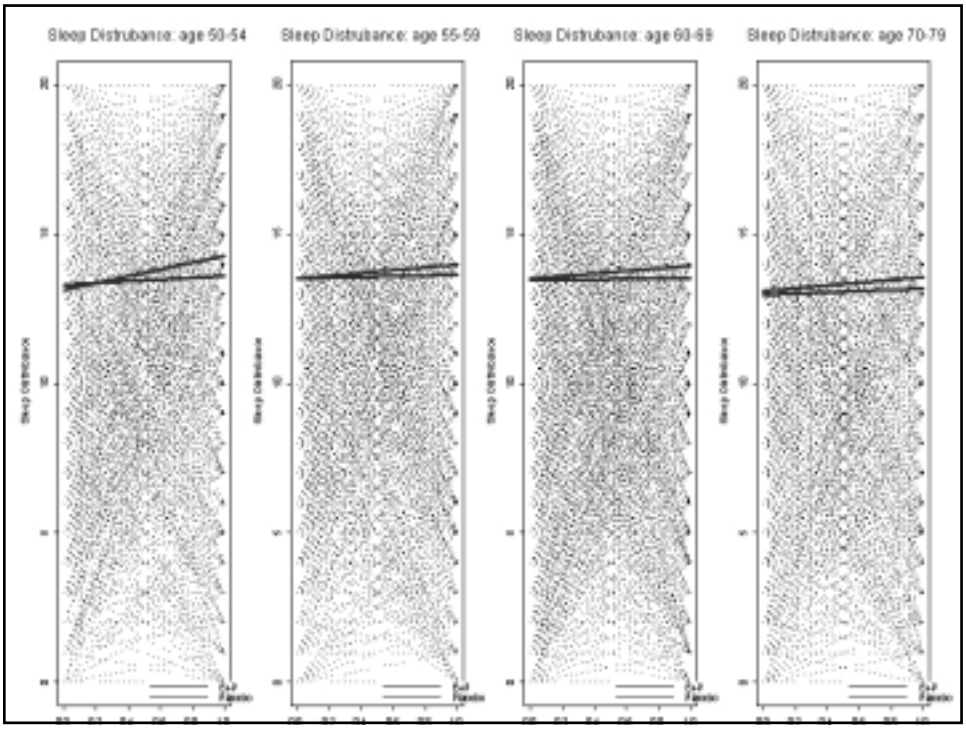
Symptoms Improvement at Year 1:
Women with Baseline Vasomotor Symptoms

	E+P (%)	Placebo (%)	p-value
n	1072	974	
Hot flashes	76.7	51.7	p<.001
Night sweats	71.0	52.8	p<.001

Women aged 50-54 with Vasomotor Symptoms

QOL measures	Mean	S.E.	P-value
Physical health	1.2	1.3	0.38
Role Physical	-1.8	3.1	0.54
Bodily Pain	1.3	1.9	0.50
Energy/Fatigue	-1.1	1.7	0.53
Social Functioning	-4.0	2.1	0.06
Role Emotional	-5.2	3.5	0.14
Mental Health	0.6	1.4	0.68
Sleep Disturbance	1.0	0.4	0.02
Satisfaction with sex	0.2	0.1	0.06





Limitations of HQOL Findings

- Peri-menopausal women not in sample: WHI not a study of symptom treatment
- Women unwilling to be randomized not in sample
- There may be quality of life benefits that we did not measure
- Not applicable to women on estrogen alone

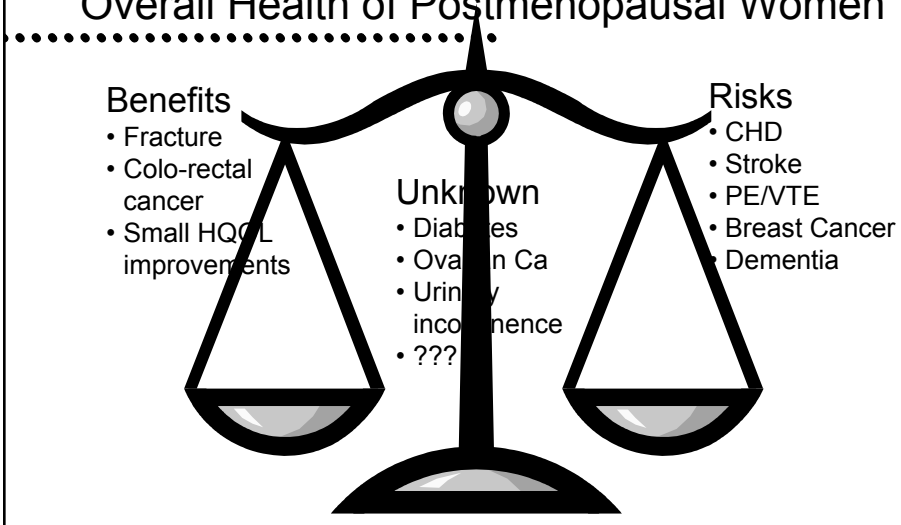
Summary of Findings

- Estrogen plus progestin had no clinically meaningful effects on postmenopausal women after one year
- No effects observed after 3 years
- Improvement in symptoms did not translate into measurable improvements in everyday life
- Only effect among younger, symptomatic women was small improvement in sleep

Clinical Implications

- Effects on quality of life would not outweigh small but significant health risks for most postmenopausal women
- Not effective for long-term use
- Minority of postmenopausal women seek treatment for menopause symptoms
- No compelling HQOL evidence to support E+P use

The Balance of Risks and Benefits on the Overall Health of Postmenopausal Women

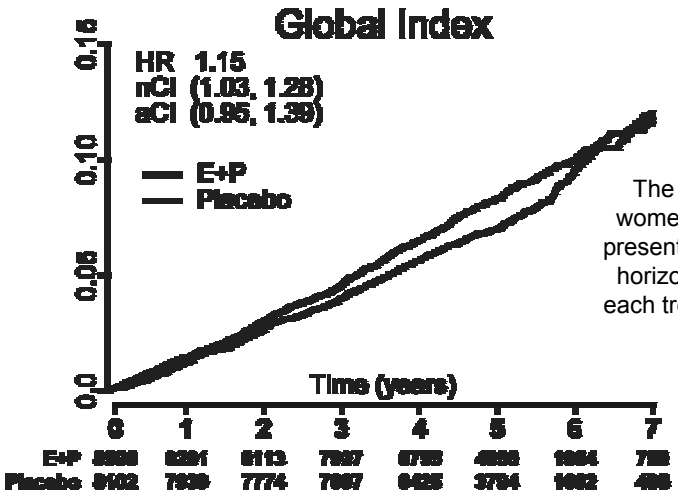


WHI Estrogen+Progestin Trial Global Index

- Purpose: to summarize important aspects of health benefits vs. risks
- Defined for each woman as the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer, colorectal cancer, hip fracture or death from other causes

WOMEN'S HEALTH INITIATIVE

Kaplan-Meier Estimates of Cumulative Hazards for the Global Index



The number of women at risk are presented below the horizontal axis for each treatment arm.

WOMEN'S HEALTH INITIATIVE

Clinical Outcomes (Annualized Percentage) by Randomization Assignment

Global Index

	Estrogen + Progestin		Placebo		Ratio
Age					
50 - 59	**142**	**(0.92%)**	**115**	**(0.80%)**	**1.16**
60 - 69	**339**	**(1.72%)**	**271**	**(1.48%)**	**1.18**
70 - 79	**270**	**(3.03%)**	**237**	**(2.76%)**	**1.10**

WOMEN'S HEALTH INITIATIVE

Global Index: Questions of Interest

1. Are there subgroups of WHI participants for whom the global index indicates greater benefit than risk?
2. How would the global index perform if additional disease events (and perhaps symptomatic conditions) were added to it?
3. What does the global index show for younger women with moderate or severe vasomotor symptoms?

Global Index Analyses: Statistical Issues

1. In a trial with multiple outcomes, it is important to specify the primary outcome.
2. Issues of multiplicity arise when one explores alternative outcomes, creative compositions of outcomes.
3. So far, global endpoints have not taken into account the relative importance of the individual diseases included in terms of their “life impact.”

Global Index Analyses: Statistical Issues

4. Using time to first event survival analysis can allow a more common, but less severe outcome to obscure/overpower findings for more severe, but less common outcomes.
5. Post hoc manipulation of global outcomes is quite subject to "manipulative instincts." (Pocock, 1997)

Global Index Analyses: Philosophical Issues

1. Choice of effect measures (absolute vs. relative risk), subgroups examined, diseases included can all be manipulated to distort the findings in a desired direction.
2. The statistical issues and any implicit manipulative distortions are mostly lost on clinicians and the public who seek a clear bottom-line message on risk vs. benefit.

WHI Global Index Analyses: Future Directions

1. Perform selected subgroup analyses.
2. Consider an "expanded" global index that incorporates life threatening diseases shown to be related E+P treatment assignment in our WHI priority papers.
3. Apply new statistical techniques to:
   - "weight" the components of the expanded global index to account for differing disease severity using 5-year case-fatality rates.
   - analyze each event separately, then combine results, instead of time to first event.

"There is considerable merit in drawing up predefined strategies for statistical analysis and reporting of trials with appropriate predeclaration of priorities, since there is a clear need to safeguard against manipulation post hoc emphases and distortions in the conclusions. However, at the same time we need to avoid becoming too inflexible by suppressing validly creative statistical and clinical science since trials will sometimes produce unpredicted and surprising findings which it would be inappropriate to suppress."

Stuart J. Pocock, 1997

Source: Pocock SJ. Clinical trials with multiple outcomes. Controlled Clin Trials 1997;18:530-545.